UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/311,720	05/14/1999	GREGORY M. GLENN	PM254809	1614

7590 10/23/2002

GARY R TANIGAWA
NIXON & VANDERHYE
1100 NORTH GLEBE ROAD
8TH FLOOR
ARLINGTON, VA 22201-4714

EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	**PAPER NUMBER**
1632	12

DATE MAILED: 10/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/311,720	Glenn et al.
Examiner	**Art Unit**
Joseph T. Woitach	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 17, 2002*

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-127* is/are pending in the application.

4a) Of the above, claim(s) *, 38, 42, 43, 47-54, 59-71, 73 , 74* is/are withdrawn from consideratio

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-31, 35, 36, 39-41, 44-46, 55-58, 72, and 75-127* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examine

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Please note that the Examiner of record and art unit has changed. The Examiner of record is now **Joseph T. Woitach** and the group art unit is now **1632**.

This application filed May 14, 1999, is continuation in part of 08/749,164 filed November 14, 1996, now US patent 5,910,306, which claims benefit to provisional application 60/086,196 filed May 21, 1998.

Applicants' amendment filed July 10, 2001, paper number 11 has been received and entered. The specification has been amended. Claims 1, 80 and 93 have been amended. Claims 102-116 have been added. Applicants' amendment filed March 14, 2002, paper number 19, has been received and entered. The title has been amended. Claims 1, 14, 37, 38, 41-44 have been amended. Claims 117-127 have been added. Claims 1-127 are pending and currently under examination.

Response to request for interference

Applicants' request to invoke an interference with US Patent 6,087,341 is noted. Consideration of Applicants' request will be made once allowable claims have been identified.

Election/Restriction

Applicant's election with traverse of species: i) sequestrin; ii) CpG1; and iii) an adenoviral regulatory region, filed July 17, 2002, paper number 21 is acknowledged. The traversal is on the ground(s) that search and examination of all claims in the same the patent application would not be an undue burden pointing to US Patents 6,087,341 and 6,348,450 (it is noted that these applications were filed by different inventors). Further, it is argued that withdrawal of the restriction requirement will provide compact prosecution and serve public interest in determining the priority claim of the instant application in an interference. See Applicants' amendments filed March 14, 2002, paper number 19, top of page 4 and July 17, 2002, paper number 21, pages 1-2. It is noted that the election of species is made with traverse, however no specific argument or evidence is presented demonstrating that the species are not patentably distinct or obvious variants of each other. See Applicants' amendment filed July 17, 2002, paper number 21, page 1. Applicants' arguments have been fully considered but not found persuasive.

This is not found persuasive because the arguments concerning alleged benefits to the public are not probative, and the alleged relatedness of the instant claimed subject matter and that of the indicated US Patents is not the same. The instantly claimed invention is directed to a method of immunization wherein the allowed claims are directed to methods of inducing an immune response (see claim 1 of 5,910,306). Further, as noted in the restriction requirement mailed June 17, 2002, paper number 20, the separate species comprise different antigens and

promoters from unrelated sources, and the use of a different adjuvant, each require a different search and consideration. Additionally, for a proper consideration and examination, each possible combination comprising each species would have to be made requiring consideration of an enormous number of possible combinations. Further, each species represents an embodiment with a separate classification requiring different searches that are not co-extensive. Finally, Applicants have not provided any arguments in their election to why each of the specific species are obvious variants or why they are not patentably distinct. Therefore, for the reasons above the restriction requirement is still deemed proper and is therefore made **FINAL.**

Claims 1-127 are pending. Claims 32-34, 37, 38, 42, 43, 47-54, 59-71, 73, 74 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 20. Claims 1-31, 35, 36, 39-41, 44-46, 55-58, 72, 75-127 are under examination as they are drawn to the elected species i) the antigen sequestrin; ii) the adjuvant CpG1; and iii) an adenoviral regulatory region for the expression of antigen.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The second application (which is called a continuing application) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht*, 168 USPQ 293 (CCPA 1971).

In the instant case, upon review of the parental continuation in part applications listed in the priority statement, specific support for the elected subject matter presently under examination is not found. Specifically, the present application is related to early filed applications as continuations in part and review of the applications and patents included in the priority claim do not provide support for the elected species of sequestrin. Additionally, given the enormous number of possible combinations for a particular antigen and adjuvant and means to administer these, *i.e.* as proteins or expressed product-including any possible type vector, none of the previous applications provide specific support for the instantly elected combination. It is noted that while the instant application provides literal support for each of the elected species , as indicated in Applicants' election, the literal support for each of the species is found throughout the application, and not present as one specifically contemplated combination. Because support for the elected species sequestrin is found first in the present application, priority of the present claims is accorded the filing date of the provisional application filed May 21, 1998.

Information Disclosure Statement

The information disclosure statements filed December 29, 1999, paper number 4, March 24, 2000, paper number 6, July 10, 2001, paper number 13, and March 14, 2002, paper number 18, fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Claim objections

The claims are objected to for the following informalities: Applicants election of species: i) sequestrin; ii) CpG1; and iii) an adenoviral regulatory region, is noted, however independent claims 1, 80, 93, 102, 110, 112, 115 and 117 are only drawn generically to the specific elected species. The independent claims should be amended to reflect the elected invention.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-31, 35, 36, 39-41, 44-46, 55-58, 72, 75-127 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing an immune response in a mammal comprising the steps: providing a polynucleotide construct comprising adenoviral regulatory region operatively linked to a polynucleotide; administering said construct to a mammal wherein administration results in the expression of said construct and production of a sequestrin polypeptide and induces an immune response in said mammal to said encoded sequestrin, does not reasonably provide enablement for a method of immunization. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the

relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The present claims are drawn broadly to methods of immunization, however it is noted that the subject of the instant rejection is the invention as it is drawn to the elected species of i) the encoded antigen sequestrin; ii) the adjuvant CpG1; and iii) an adenoviral regulatory region for control of the expression of sequestrin. With respect to claims 1 and 80, and their dependent claims, the term immunization is given its art accepted meaning of providing protection to an individual. This interpretation is further supported by dependent claims 17, 83-86 which recite a prophylactic response and claims 99-101 which recite a vaccine. Remaining claims are drawn to inducing an immune response or only for delivery, however dependent claims clearly indicate that the immune response has a biological effect (claim 115) or is protective (claim 124). Upon review of the present specification, in particular the field of the invention (page 1; lines 15-19) and description of the invention, the only proposed effect and use of the instantly invention is for the immunization of a subject. It is noted that claims 102-127 which were added after the filing of the present application are drawn more broadly to methods of inducing an immune response and methods of delivery. While the preamble of these claims is more broad than a method of immunization, as set forth in the original claims 1-101, the general support for the recitation has been accorded to these terms because the method of immunization requires the delivery and induction of an immune response. However, upon review of the disclosure, specific support for

these general methods can not be found, and thus, the claims are being interpreted to encompass methods of immunization as taught throughout the entire specification.

With respect to the specific elected species of i) the encoded antigen sequestrin; ii) the adjuvant CpG1; and iii) an adenoviral regulatory region for control of the expression of sequestrin the specification provides literal support for each of these embodiments, however the support is provided as separate and distinct portions of the specification. The closest example of the elected invention is provided by Example 19 (pages 67-69) where a plasmid encoding a truncated recombinant sequestrin protein and cholera toxin as an adjuvant was administered using an epidermal gene gun delivery system. Support for CpG acting as an adjuvant can be found in Examples 34 and 38. None of the working examples provide the use of an adenoviral vector system or regulatory region, however general support for its use is provided on page 13, lines 22-23 as "[U]seful vaccine vectors".

Sequestrin is a protein found on the human malaria parasite *Plasmodium falciparum* (Ockenhouse *et al.* PNAS page 3174, first column). Ockenhouse *et al.* propose that sequestrin may be "a good candidate for a vaccine component" based on their results with anti-idiotype antibodies. However, while the malaria parasite has been more extensively studied since the results of Ockenhouse *et al.*, presently the art teaches that no vaccine for malaria exists. Two points of enablement are at issue; first, the specification demonstrates that antisera to sequestrin can be generated, however it is unclear if the immune response is prophylactic. The art teaches one can produce an immune response when one injects enough of almost any protein. However,

the specification does not that the immunogenic epitope or other portions of sequestrin produces a prophylactic immune response to *P. falciparum* as encompassed by the full scope of the claim. Finally, the claimed vaccine is a DNA vaccine, and the specification relies in great part on delivery methods and expression systems taught by others for the ability to infect the host cells and for the production of the proper amount of the foreign protein to induce an immune response, however the specification lacks the necessary guidance or demonstration that these methods and systems can be used for expression of the proposed open reading frames which result in a prophylactic immune response.

The present specification provides evidence that an immune response to sequestrin can be generated, however as noted by Ockenhouse *et al.* difficulties in identifying strain-invariant binding domains and poor immunogenicity has hampered the characterization of *P. falciparum* (page 3179, first paragraph) and thus, the development of potential vaccines. The results of Ockenhouse *et al.* provide evidence that sequestrin is surface accessible and that it binds CD36 on human cells. Further, the results demonstrate that anti-idiotype antibodies may be useful in providing passive immunity by blocking the binding of the cytoadherent protein, however in the evaluation of serologically defined epitopes it is demonstrated that immune sera is strain specific. Further, it is taught that this implies that there is either an antigenitic diversity among the parasites which results in multiple variants of sequestrin or that a structurally conserved domain is poorly immunogenic. In either case, while sequestrin may be an accessible surface protein, no evidence exists to date that it will serve as a proper antigen in a vaccine formulation. Further,

given the potential for strain diversity, the specification fails to provide the necessary guidance to identify other sequestrin sequences in order to test the variants for their potential to serve as a vaccine. As noted above, presently the art teaches that a vaccine for malaria does not exist. It is not necessary to know the function of a protein or even the exact immunogenic fragment which is recognized in subject, however given the art recognized difficulties in producing effective vaccines the specification must provide the necessary guidance to appropriate antigens which will serve to produce a prophylactic immunological response. The antisera from individuals clearly indicates that a developed immunity varies among individuals and strains and that none of the developed immune response result in a protective immunity. Given the lack of an effective malaria vaccine today, there is no clear indication that use of the encoded protein from any proposed reading frame of sequestrins would serve as a potential vaccine to *P. falciparum*. The specification does not clearly teach how to use the described polynucleotide to define immunogenic epitopes, nor does it provide the guidance or the exemplification that the sequences can be used as a vaccine against *P. falciparum*.

Finally, the specification relies on the vector systems and methods of others for the administration and expression of the encoded protein for use in a DNA vaccine. It is well established in the art that one can use a virus to immunize a subject to produce an immune response, it is often necessary, as in the examples of the present application, to re-administer "booster shots" to stimulate the desired immune response. However, it is not clear from the guidance in the specification, the art of record nor the present state of art how one would produce

the effects of immunization through the methods recited in the claim. It is clear that there is an immune response to *P. falciparum* after infection as evidenced by antisera in a subject, however, there is no demonstration that other forms of immune response such as CTL response or stimulation of NK cells was or could be stimulated by the recited method. The humoral immune response which produces IgA and IgG can be generated simply by injecting the foreign protein into an animal. A cellular immune response necessary for a prophylactic effect, however, is more complicated and dependent on appropriate expression levels in a antigen-presenting cell. Therefore, it is unclear from the guidance and examples given in the specification which host cells would serve as appropriate cells for use in the induction of other immune responses, such as CTL, in a subject. Further, McCluskie *et al.* (Molecular Medicine, 1999) teach that the route and method of delivery of a DNA vaccine influences the immune response. In particular, results obtained in animal models is not predictive of results or the effectiveness in other subjects (page 288, second column in results section). There are several art recognized limitations and unpredictability issues regarding the delivery of a polynucleotide as a DNA vaccine, that include: vector to be used for gene expression, production of effective concentration of the candidate protein, delivery of the protein or gene to target cell, sustained expression and production of the candidate protein *in vivo*, and maintaining an effective level of the protein *in vivo* in order to produce an effective immune response. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). In the instant case, Applicants have proposed using sequestrin as a potential vaccine against malaria however, essentially all of the work required to ultimately

define and develop the necessary sequences and methods to produce a prophylactic immune response has been left for others.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

Conclusion

No claim is allowed.

The claims are free of the art of record because while each of the elected species were described in the art as known proteins, adjuvant, promoters, the art fails to provide adequate motivation to combine these three specific elements into a formulation to generate a vaccine or in to use them in a method of immunization. The closest prior art drawn to Applicants' invention is provided by Khavari *et al.* (US Patent 6,087,341) which teaches methods of inducing an immune response using a polynucleotide vector to express the antigen. However, Khavari *et al.* do not disclose to use the particular combination of elected species of elements or provide support for their ability to serve as a vaccine in immunization protocols.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached at (703)305-4081.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist Pauline Farrier whose telephone number is (703)305-3550.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Deborah Crouch

Joseph T. Woitach

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800/630